

## Localized Limb Cutaneous Metastases

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Cutaneous metastatic disease may be evident in a variety of forms and locations. Anatomically, it may on occasion be confined as localized limb metastases. We report on two patients with localized limb metastases, one from melanoma and the other from Merkel cell carcinoma. Patients with localized limb metastasis have a poor prognosis; however, treatment options not available for generalized cutaneous metastatic disease, such as amputation or isolated limb perfusion with chemotherapeutic agents, can be at times be beneficially employed.

*J. Surg. Oncol.* 1998;67:261–264. © 1998 Wiley-Liss, Inc.

**KEY WORDS:** Merkel cell carcinoma; melanoma; limb; metastases

### INTRODUCTION

Cutaneous metastatic disease may display a wide variety of different appearances and anatomic locations [1–12]. Metastases to upper extremities are not common and usually appear as late findings. These are most often due to melanoma, but may be from carcinoma of the breast, lung, kidney, and colon. The lower extremities are a less likely site, with melanoma most common and cancer from the lung and kidney less frequent. Localized limb metastases represent a special challenge. We report on two patients, one with Merkel cell carcinoma and the other with melanoma, both of which were originally evident as localized limb metastases, and discuss the differential diagnosis and treatment options.

### CASE REPORTS

#### Case 1

A 74-year-old man was seen for evaluation of an enlarging nodule on his right lower leg. He had allowed it to grow to a size of 5–6 cm. A skin biopsy specimen demonstrated a tumor composed of basophilic staining cells organized in a trabecular pattern in the dermis. Numerous mitotic figures were seen. The tumor cells stained with a perinuclear dot pattern with cytokeratin, the characteristic pattern of a Merkel cell carcinoma (Fig. 1). An inguinal node dissection, at the time of initial presentation, demonstrated no evidence of metastatic

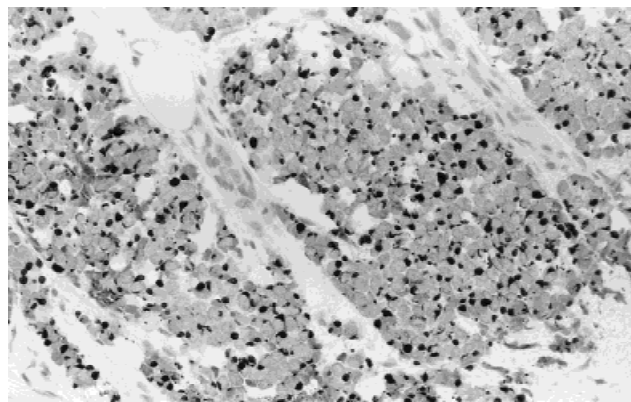


Fig. 1. Perinuclear dot cytotokeratin staining in Merkel cell carcinoma (immunoperoxidase; original magnification  $\times 33$ ).

spread. However, during the next year, five separate tumors developed on the right lower extremity, all of which were excised (Fig. 2a,b). The patient did well for the subsequent 10 years. A computed tomographic (CT) scan

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Accepted 30 December 1997

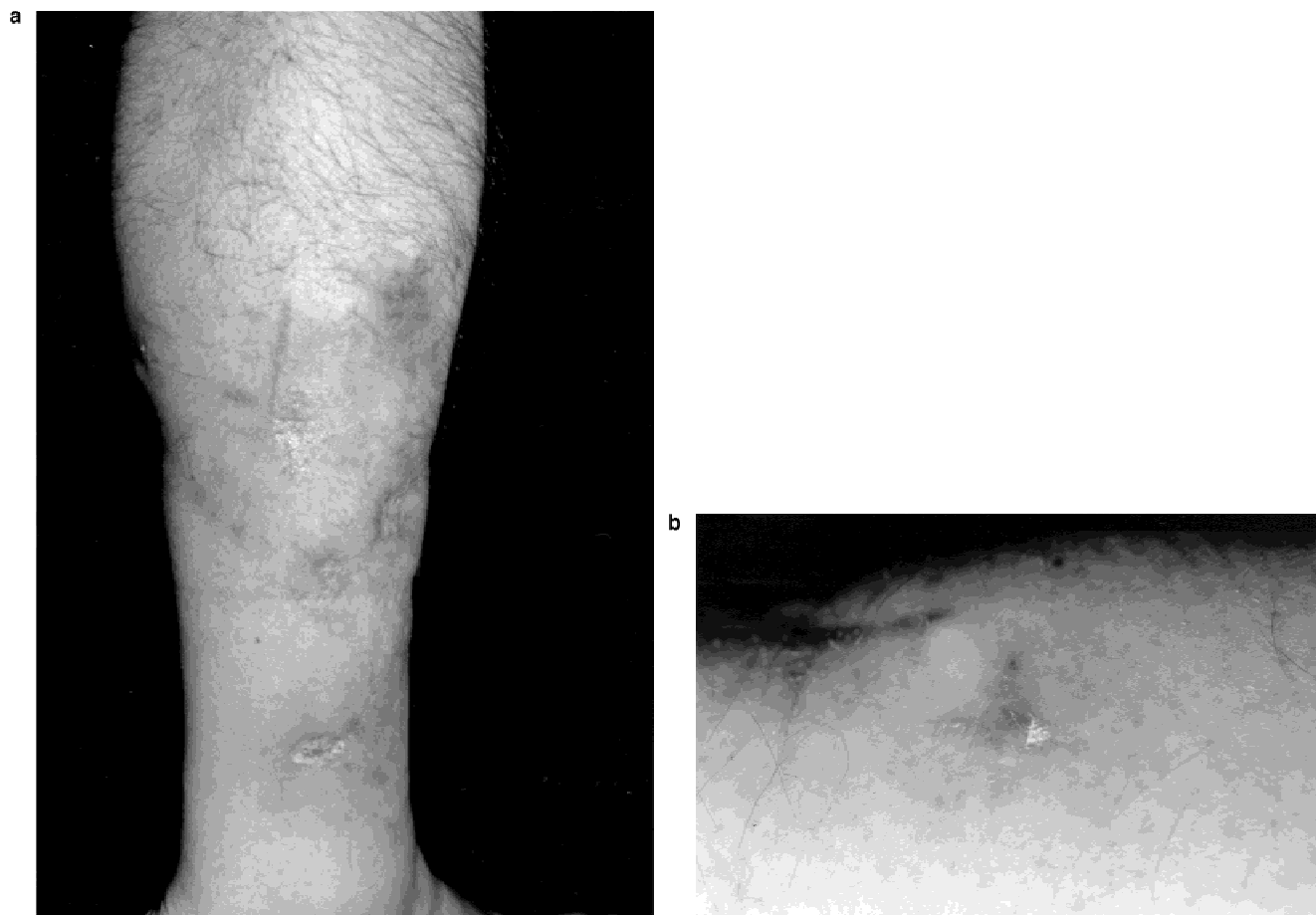


Fig. 2. **a:** Numerous scars from prior excisions of Merkel cell carcinoma. **b:** Recurrent Merkel cell carcinoma within a scar

of the abdomen 10 years after initial presentation did not demonstrate metastatic spread; however, 11½ years after the initial presentation he developed metastatic lesions on the groin and abdominal walls, and continued to develop cutaneous lesions on his limbs. Currently, he is receiving systemic chemotherapy.

### Case 2

A 75-year-old Caucasian woman with a prior history of endometrial carcinoma, breast carcinoma, hypertension, arrhythmias, melanoma of the temple, and diabetes mellitus was seen approximately 1 year after excision of a melanoma in the right lower leg. Examination revealed several 2 cm nodules at the margin of the graft site from the original melanoma surgery. A biopsy specimen of the nodule showed lobules composed of pleomorphic epithelioid appearing melanocytes (Fig. 3). The epidermis was uninvolved, thereby helping to confirm the clinical impression of metastatic melanoma. Subsequently, in the next few months, she developed ten nodules localized to the right lower extremity that histologically demonstrated malignant melanoma. All of these tumors were completely excised. All of the lesions, except for one that

involved the fascia, were located in the upper dermis. A CT scan has failed to identify generalized disease.

### DISCUSSION

We describe two different neoplasms that presented with localized limb metastases. Although the neoplasms arose from two distinct cell types, the Merkel cell and the melanocyte, a biological relationship between Merkel cell carcinomas and melanomas may exist. Melanocytes arise from the neural crest; it has been hypothesized that dermal Merkel cells also originate from the neural crest and migrate to the skin [13,14]. Other studies have suggested that Merkel cell tumors could arise from a pluripotential cell or from an epidermal stem cell [15]. The biological behavior of both tumors can be dismal, with approximately one-third of Merkel cell carcinomas metastasizing. The 5-year survival for Clark's level 4 melanomas is approximately 68% [16–18]. Histologically, some melanomas may predominantly be composed of small blue lymphoid cells resembling Merkel cell carcinoma [19]. Localized limb metastasis is relatively common in melanoma. In one report of 190 melanomas of the limb, regional metastases developed in 60 patients [20],

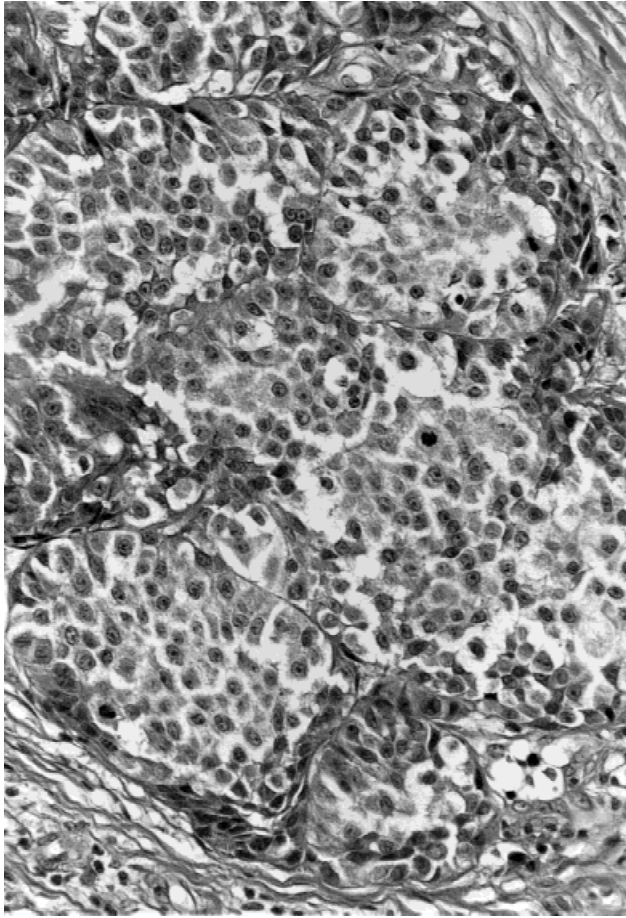


Fig. 3. Metastatic melanoma composed of nests of pleomorphic appearing epithelioid melanocytes within the dermis (hematoxylin & eosin; original magnification  $\times 60$ ).

whereas the incidence of limb metastases in Merkel cell carcinoma is unknown.

The mechanism of tumor spread has stimulated considerable interest. Tumor spread can occur along the cerebrospinal, arterial, venous, lymphatic, and interstitial circulations [21]. Most cases of limb metastases probably represent localized spread through the lymphatics. However, localized extension through interstitial plains and connective tissue is also possible. In our second case, the tumor originally was detected adjacent to a scar, making interstitial spread likely. In one of the excisions, tumor was found within the fascia, which may also represent a plain where the tumor can easily extend. Localized limb metastases may be seen with many tumors, including epithelioid sarcomas [22,23], clear cell sarcomas [24], malignant peripheral nerve sheath tumors, and porocarcinomas [25]. Spindle cell hemangioendothelioma can be evident with multiple nodules on a limb mimicking metastatic disease [26]. Although histologically distinct, these neoplasms, except for breast carcinomas, usually arise in the skin or subcutaneous tissue, and therefore the localized pattern of extension may occur because of an high

affinity for the skin. Histologically, epidermotropism can be found in porocarcinomas, Merkel cell carcinomas, and melanomas [25,27,28]. Future studies on cell surface molecules may elucidate the molecular basis for epidermotropism. An interesting observation is that expression of CD44, a cell surface marker involved in tumor stroma interaction, has been found in both Merkel cell carcinomas and melanomas with metastatic potential. [29,30]

As in generalized cutaneous metastatic disease, the prognosis of patients with localized limb metastases is poor (2,5,8–10). Since the tumor is originally localized to an extremity, treatment options not available for generalized metastatic disease include localized limb perfusion and amputation. The ability of limb amputation to cure melanoma is somewhat controversial. Recent studies have suggested that amputation should primarily be used as a palliative operation, or in patients who have failed to respond to limb perfusion and immunotherapy. [31,32] Several studies of localized limb perfusion with chemotherapeutic agents, such as melphalan and cisplatin, have been performed in patients with melanomas [33–38]. In a recent study of hyperthermic antitlastic therapy with melphalan for patients with recurrent or in-transit limb metastasis, 56% had a complete response rate; the 5-year survival was 64% [33]. Lejeune et al. reported a 91% response rate for in-transit melanomas on the limbs using isolated perfusion of the limbs with tumor necrosis factor-alpha, interferon-gamma, and melphalan [34]. Localized hyperthermic limb perfusion with melphalan has also been successful in an isolated case of Merkel cell carcinoma of a lower extremity [39]. In our patient with Merkel cell carcinoma, the disease was controlled for a few years simply by complete excision of cutaneous tumors. Merkel cell carcinomas, unlike melanomas, are radiosensitive [40], and radiation therapy is recommended as adjuvant therapy when there is evidence of angiolymphatic invasion or the tumor approaches close to the margins of resection [41–43].

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